FINAL ACTION

1. Applicant's amendments and responses filed January 3, 2008 is acknowledged. Claims 1-10 have been canceled. Claims 11-18 are under examination.

Rejections Maintained

2. The rejection under 35 U.S.C. 103(a) is maintained for claims 11 and 14-15 for the reasons set forth on pages 3-6 paragraph 3 of the previous Office Action.

The following rejection is maintained and reiterated below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11 and 14-15 are rejected under 35 U.S.C. 103(a) as unpatentable over Keen et al *(Plastic and Reconstructive Surgery, July 1994, 94, No.1, pages 94-99)* in view of Johnson et al *(U.S. Patent No. 5,512,547 published April 30, 1996).*

Claims 11 and 14-15 are directed to a method of treating a human or animal cosmetic condition treatable with a botulinum toxin neurotoxin (wrinkling or facial wrinkling, claims 14-15) comprising administering to the human or animal, a treatment effective amount of a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Keen et al teach a method of treating patients that have hyperkinetic facial lines (wrinkles) with injections of botulinum toxin A (botulinum toxin A complex)(see the Abstract and pages 95-97). Keen et al teach that the injections may be repeated to achieve the desired effect (page 98). Keen et al teach that

botulinum toxin A injections eliminated hyperfunctional facial lines (wrinkles) in healthy aesthetic surgical patients (page 94). Keen et al teach that antibodies to botulinum toxin A have been described in patients receiving much larger dosages of botulinum toxin complex for long periods of time and the antibodies can render the toxin non-effective but do not harm the patient (nonresponders) (page 98). Keen et al teach that the use of botulinum toxin A is a safe and efficacious method of nonsurgically eliminating facial wrinkles in aesthetic surgical patients for a period of 4 to 6 months (page 99).

Keen et al do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

It would be *prima facie* obvious to one of ordinary skill at the time the invention was made to substitute the botulinum toxin A (botulinum toxin A complex) in the method of treating patients with hyperkinetic facial lines (wrinkles) as taught by Keen et al with the pure botulinum toxin A (without complexing proteins) as taught by Johnson et al because Johnson et al teach that purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients. It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex) because Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield

predictable results". It well known in the art to use botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial wrinkling. Keen et al recognize that patients receiving much larger dosages of botulinum toxin complex for long periods of time may produce neutralizing antibodies to the botulinum toxin complex. Johnson et al also recognize that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is pure neurotoxin instead of the complex. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

Applicant's Arguments

Applicant urges that Keen et al and Johnson et al do not teach or suggest the instant claim limitation to administration of a *Clostridium botulinum* neurotoxin which is free of complexing proteins in subjects already exhibiting neutralizing antibodies. Applicant urges that Keen et al and Johnson et al teach subjects who have developed neutralizing antibodies would not benefit from treatment with botulinum neurotoxins. Applicant urges that column 2, lines 51-55 of Johnson et al state that " the toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective". Applicant urges that Johnson et al teach away from administering a Clostridium botulinum neurotoxin free from complexing proteins to patients who have developed neutralizing antibodies.

Applicant urges that Johnson et al actually pertains to the development of a shelf-stable botulinum neurotoxin composition for preventing the development of neutralizing antibodies. Applicant urges the Office's position that " It would

have been expected absent evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex)" finds no basis in the prior disclosure of record.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed January 3, 2008 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Keen et al teach the administration of botulinum toxin to patients for cosmetic conditions treatable by botulinum toxin (e.g. hyperfunctional facial lines (wrinkles)). Keen et al teach that patients that receive large dosages of botulinum toxin complex over long periods of time can render the toxin non-effective (e.g. these patients are non-responders). Keen et al do teach a composition of botulinum toxin that is free from complexing proteins. However, Johnson et al teach compositions of pure botulinum toxin that are free from non-complexing proteins. Johnson et al teach the compositions of the invention reduces the amount of inactive toxin in each vial and thereby lessens

the possibility of antibody formation after injection of the composition into patients. One of ordinary skill in the art would reasonably conclude that the compositions taught by Johnson et al comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. Johnson et al recognize patients that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the development of compositions comprising" essentially pure botulinum toxin". Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex. Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use botulinum toxin complex to treat cosmetic conditions such as facial wrinkling. See Keen et al. It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both Keen et al and Johnson et al. Johnson et al also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provided a solution to this problem,

by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition. It should also be noted that "obvious to try" is proper when there is a finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursed the known potential options with a reasonable expectation of success. See KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007). In the instant case, there is a need in the art to find a problem to the development of patients with neutralizing antibodies to the botulinum toxin complex. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection have failed. Johnson et al developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art. This provides further support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies to botulinum toxin complex.

In response to Applicant's comments regarding, column 2, lines 47-51 of Johnson et al, as stated above, it is the Examiner's position that Applicant has mischaracterized this passage in Johnson et al. It should be noted that this is

the Background Section of Johnson et al. In this passage, Johnson et al explain problems in the art associated with patients that have developed neutralizing antibodies to the botulinum toxin complex. Johnson et al recognized the problems associated with patients that have developed neutralizing antibodies to the complex and thus, developed compositions of "essentially pure botulinum toxin" which reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. Therefore, Johnson et al do not teach away from the claimed invention, but in fact, solve the problem associated with patients that have developed neutralizing antibodies to botulinum toxin complex.

There is nothing on the record to show that the combination of prior art reference does not teach or suggest the claimed invention.

In view of all of the above, this rejection is maintained.

3. The rejection under 35 U.S.C. 103(a) is maintained for claims 11-15 for the reasons set forth on pages 6-10 paragraph 4 of the previous Office Action. The following rejection is maintained and reiterated below:

Carruthers et al teach a method of treating cosmetic conditions such as glabellar frown lines Crow's feet and horizontal forehead lines, (all forms of wrinkles) by administering botulinum toxin A complex (Botox® and Dysport®) (pages 210 and 214-230, See for example page 215, Figure 1). Carruthers et al teach that incidence of treatment resistance to botulinum toxin A usually varies with the amount of exposure to the toxin (page 212). Carruthers et al teach that in neurologic patients, it is estimated that one-third of all treatment failures may be the result of the development of antibodies (page 214). Carruthers et al teach that patients injected toxin doses greater than 100 units/session, patients receiving booster injections within 30 days of initial botulinum toxin injection and

injection of toxin into systemic circulation may develop antibodies against botulinum toxin A complex (page 213).

Carruthers et al teach do not teach the claim limitation "the cosmetic wherein the cosmetic treatment is for hyperhidrosis (excessive sweating, a cosmetic condition).

Heckman et al teach that after 1-year follow-up of patients that received 500 U per axilla of botulinum toxin injection for axillary hyperhidrosis, 3 out of 12 patients showed mitigated recurrence of axillary hyperhidrosis after 3, 4 and 7 months, respectively, which could be overcome by a second injection of botulinum toxin (page 1298).

Carruthers et al and Heckman et al teach do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the botulinum toxin A (botulinum toxin A complex) in the method of treating patients with hyperhidrosis as taught by Carruthers et al and Heckman et al with the pure botulinum toxin A (without complexing proteins) as taught by Johnson et al because Johnson et al teach that purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients. It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex) because Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is

beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial wrinkling. Carruthers et al recognize that patients receiving much larger dosages of botulinum toxin complex for long periods of time may produce neutralizing antibodies to the botulinum toxin complex. Johnson et al also recognize that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is pure neurotoxin instead of the complex. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed January 3, 2008 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Carruthers et al teach the administration of botulinum toxin to patients for cosmetic conditions treatable by botulinum toxin (e.g. glabellar frown lines (wrinkles), Crow's feet and horizontal forehead lines). Carruthers et al teach that patients that receive large injections within 30 days of the initial toxin injection and injections into systemic circulation may develop neutralizing antibodies (e.g. these patients are non-responders). Heckman et al

teach that botulinum toxin is used to treat hyperhidrosis. Carruthers et al and Heckman et al do teach a composition of botulinum toxin that is free from complexing proteins. However, Johnson et al teach compositions of pure botulinum toxin that are free from non-complexing proteins. Johnson et al teach that compositions of the invention reduce the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. One of ordinary skill in the art would reasonably conclude that the compositions taught by Johnson et al comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. Johnson et al recognizes patient that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the developed compositions of "essentially pure botulinum toxin". Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex. Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial

wrinkling. See Heckman et al and Carruthers et al, respectively. It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both Carruthers et al and Johnson et al. Johnson et al also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition. It should also be noted that "obvious to try" is proper when there is a finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursed the known potential options with a reasonable expectation of success. See KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007). In the instant case, there is a need in the art to find a problem to the development of patients with neutralizing antibodies to the botulinum toxin complex. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection have failed. Johnson et al developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art. This provides further

support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies to botulinum toxin complex.

In response to Applicant's comments regarding, column 2, lines 47-51 of Johnson et al, as stated above, it is the Examiner's position that Applicant has mischaracterized this passage in Johnson et al. It should be noted that this is the Background Section of Johnson et al. In this passage, Johnson et al explains the problems in the art associated with patients that have developed neutralizing antibodies to the botulinum toxin complex. Johnson et al recognized the problems associated with patients that have developed neutralizing antibodies to the complex and thus, developed compositions of "essentially pure botulinum toxin" which reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. Therefore, Johnson et al do not teach away from the claimed invention, but in fact, solve the problem associated with patients that have developed neutralizing antibodies to botulinum toxin complex.

There is nothing on the record to show that the combination of prior art reference does not teach or suggest the claimed invention.

In view of all of the above, this rejection is maintained.

4. The rejection under 35 U.S.C. 103(a) is maintained for claims 16-18 for the reasons set forth on pages 10-13, paragraph 5 of the previous Office Action. The following rejection is maintained and reiterated below:

Kessler et al teach long-term treatment of cervical dystonia (CD) with botulinum toxin A (see the Title and the Abstract). Kessler et al teach that the only risk of botulinum toxin injections is the development of serum antibodies against the toxin (see the Abstract).Kessler et al teach that 2% of patients of the study developed neutralizing antibodies (see Abstract). Kessler et al teach that among the 162 patient who discontinued therapy, 17 reported having lost their initially beneficial effect (page 271). Kessler et al teach that at least one of the tests performed detected neutralizing serum antibodies in 9 of the 17 patients who clinically fulfilled the criteria for secondary nonresponse (page 271). Kessler et al teach that secondary nonresponse is one of the major problems in long-term treatment of CD with botulinum toxin A because it entails discontinuing, depriving the patient of the most successful therapy available (page 272). Kessler et al teach that this study confirms that patients at risk of developing neutralizing antibodies are those with high doses administered at relatively short intervals which is in good agreement with previous studies on the issue (page 273).

Kessler et al do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the botulinum toxin A (supplied by Dysport, Speywood, U.K. botulinum toxin A complex) in the method of treating patients with cervical dystonia as taught by Kessler with the pure botulinum toxin A (without complexing proteins) as taught by Johnson et al because Johnson et al teach that purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients. It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are secondary nonresponders (have neutralizing antibodies to botulinum toxin A complex) because Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be

obviously desirable to have higher specific activity preparations than those currently available (column 2).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial wrinkling. Kessler et al recognize that patients receiving much larger dosages of botulinum toxin complex for long periods of time may produce neutralizing antibodies to the botulinum toxin complex. Johnson et al also recognize that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is pure neurotoxin instead of the complex. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed January 3, 2008 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Kessler et al teach the administration of botulinum toxin to patients for dystonia or a nervous system disorder treatable by botulinum toxin (e.g. cervical dystonia (CD)). Kessler et al teach that patients receiving

botulinum toxin injections have risk of developing neutralizing antibodies to the botulinum toxin complex (e.g. these patients are non-responders). Kessler et al do teach a composition of botulinum toxin that is free from complexing proteins. However, Johnson et al teach compositions of pure botulinum toxin that are free from non-complexing proteins. Johnson et al teach the compositions of the invention reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. One of ordinary skill in the art would reasonably conclude that the compositions taught by Johnson et al comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. Johnson et al recognize patients that have developed neutralizing antibodies to the complex are a growing concern the art, thus this is the very bases for the development of compositions comprising "essentially pure botulinum toxin". Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex. Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use botulinum toxin complex to

treat dystonia or a nervous system disorder such as dystonia. See Kessler et al. It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both Kessler et al and Johnson et al. Johnson et al also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provided a solution to this problem, by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition. It should also be noted that "obvious to try" is proper when there is a finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursed the known potential options with a reasonable expectation of success. See KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007). In the instant case, there is a need in the art to find a problem to the development of patients with neutralizing antibodies to the botulinum toxin complex. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection have failed. Johnson et al developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the

prior art. This provides further support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies to botulinum toxin complex.

In response to Applicant's comments regarding, column 2, lines 47-51 of Johnson et al, as stated above, it is the Examiner's position that Applicant has mischaracterized this passage in Johnson et al. It should be noted that this is the Background Section of Johnson et al. In this passage, Johnson et al explain the problems in the art associated with patients that have developed neutralizing antibodies to the botulinum toxin complex. Johnson et al recognized the problems associated with patients that have developed neutralizing antibodies to the complex and thus, developed compositions comprising "essentially pure botulinum toxin" which reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. Therefore, Johnson et al do not teach away from the claimed invention, but in fact, solve the problem associated with patients that have developed neutralizing antibodies to botulinum toxin complex.

There is nothing on the record to show that the combination of prior art reference does not teach or suggest the claimed invention.

In view of all of the above, this rejection is maintained.

5. The rejection under 35 U.S.C. 103(a) is maintained for claims 16-18 for the reasons set forth on pages 13-16, paragraph 6 of the previous Office Action. The following rejection is maintained and reiterated below:

Goschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages 98-99 and Table 3, page 101). Goschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A complex (pages 98-99 and Table 3, page 101). Goschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goschel et al teach that based on theses studies, second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102).

Goschel et al do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Johnson et al teach a pharmaceutical composition comprising an essentially pure botulinum toxin A (see the Abstract and column 2). Johnson et al teach that the use of pure neurotoxin instead of the toxin complex, which is used commercially, reduced the amount of toxin required to obtain the necessary number of active U per vial as mandated by the U.S. Food and Drug Administration (column 2). Johnson et al teach that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients (column 2). Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the botulinum toxin A (botulinum toxin A complex) in the method of treating patients with a dystonia or a nervous system disorder treatable with botulinum neurotoxin as taught by Goschel et al with the pure botulinum toxin A (without complexing proteins) as taught by Johnson et al because Johnson et al teach that purified product reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients. It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex) because Johnson et al teach that higher specific activity preparations reduce the probability of patients developing neutralizing antibodies and it would be obviously desirable to have higher specific activity preparations than those currently available (column 2).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar

methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use botulinum toxin complex to treat cosmetic conditions such as hyperhidrosis and facial wrinkling. Goschel et al recognize that patients receiving much larger dosages of botulinum toxin complex for long periods of time may produce neutralizing antibodies to the botulinum toxin complex. Goschel et al even suggest that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions. Johnson et al also recognize that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provide a solution to this problem, by preparing a product that is pure neurotoxin instead of the complex. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed January 3, 2008 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Goschel et al teach the administration of botulinum toxin to patients with dystonia or a nervous system disorder treatable by botulinum toxin (e.g. torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients). Goschel et al teach some patients develop neutralizing antibodies and these neutralizing antibodies cause therapeutic failure (these patients are non-responders). Goschel et al do not specifically teach a composition of botulinum toxin that is free from complexing proteins. However, Johnson et al teach compositions of pure botulinum toxin that are free form non-complexing proteins. Johnson et al teach the compositions of the invention reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. One of ordinary skill in the art would reasonably conclude that the compositions

taught by Johnson et al comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. Johnson et al recognizes patient that have developed neutralizing antibodies to the complex are a growing concerning the art, thus this is the very bases for the development of compositions comprising "essentially pure botulinum toxin". Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex. Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use botulinum toxin complex to treat dystonia or a nervous system disorders. See Goschel et al. It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both Goschel et al and Johnson et al. Johnson et al also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. Johnson et al provided a solution to this problem, by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin

(e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition. It should also be noted that "obvious to try" is proper when there is a finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursed the known potential options with a reasonable expectation of success. See KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007). In the instant case, there is a need in the art to find a problem to the development of patients with neutralizing antibodies to the botulinum toxin complex. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection have failed. Johnson et al developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art. This provides further support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies to botulinum toxin complex.

In response to Applicant's comments regarding, column 2, lines 47-51 of Johnson et al, as stated above, it is the Examiner's position that Applicant has mischaracterized this passage in Johnson et al. It should be noted that this is the Background Section of Johnson et al. In this passage, Johnson et al explain the problems in the art associated with patients that have developed

neutralizing antibodies to the botulinum toxin complex. Johnson et al recognized the problems associated with patients that have developed neutralizing antibodies to the complex and thus, developed compositions comprising "essentially pure botulinum toxin" which reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the composition into patients. Therefore, Johnson et al do not teach away from the claimed invention, but in fact, solve the problem associated with patients that have developed neutralizing antibodies to botulinum toxin complex.

There is nothing on the record to show that the combination of prior art reference does not teach or suggest the claimed invention.

In view of all of the above, this rejection is maintained.

Status of Claims

6. No claims allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
April 10, 2008

/Shanon A. Foley/

Supervisory Patent Examiner, Art Unit 1645